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RITTER-REACTION ON STEROIDS[1,2]
RING EXPANSION OF STEROID OXETHANS INTO DIHYDROOXAZINES

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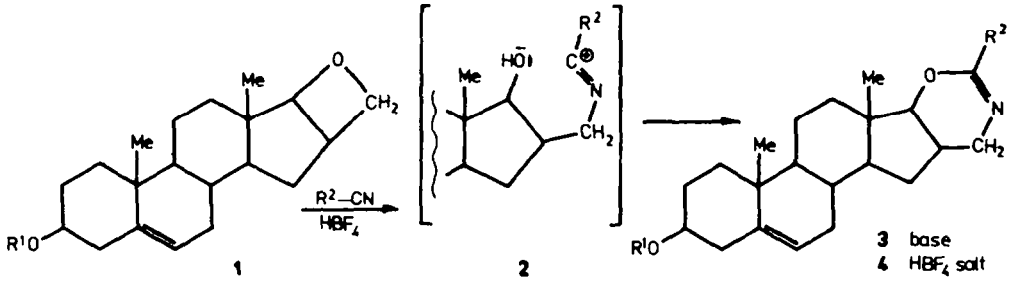
ABSTRACT — The 3β-acetoxy-16β,17β-epoxymethyleneandrost-5-ene (1) transforms into the dihydrooxazine condensed to the sterane skeleton (4a,b,c,e,g,i) in a ring-expansion reaction with alkyl and aryl nitriles in the presence of HBF_4 — diethyletherate The 3β-acetoxy-16α,17α-epoxymethyleneandrost-5-ene (9) undergoes a Wagner-Meerwein rearrangement under similar conditions

Acid nitriles yield acylamino derivatives with all organic compounds forming carbonium cations in strongly acid media. This reaction recognized by Ritter et al.[3-5] results in the vicinal diaxial trans-acylamino compound in the case of steroid epoxides Such stereospecific ring cleavage of steroid epoxides have been realized with 2β,3β-epoxycholestan, 3β-substituted 4α,5α- and 4β,5β-epoxycholestan, as well as 5α,6α- and 5β,6β-epoxycholestan and androstane derivatives in acetonitrile employing $HClO_4$ [6-9] Analogous conversion of epimeric 5,6-epoxycholestans in acetonitrile on the effect of BF_3 — diethyletherate yields similar products.[10] In the case of 6β-substituted cholestan epimers, position isomers of the acetylaminohydroxy type were obtained [11] The ring cleavage of 5,6-epoxycholestan epimers has also been effected with benzonitrile [12] This reaction of some 9β,11β-epoxysteroids is also known.[13-15]

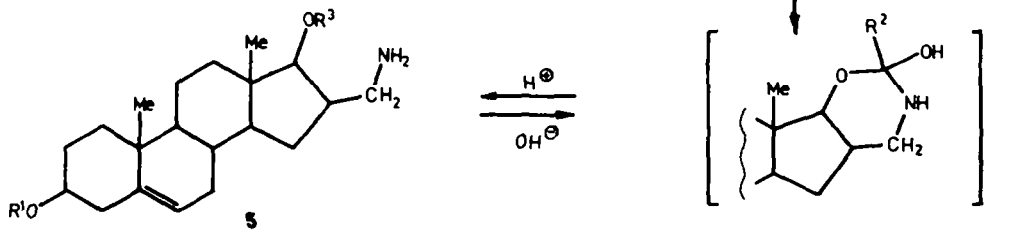
While the stereospecific reactions of epoxides condensed to the six-membered rings in the sterane skeleton result in the corresponding trans-acylaminohydroxysteroids in a satisfactory yield, the ring cleavage of epoxides condensed to the five-membered ring D is accompanied by several side-reactions. It was observed recently that of the 16,17-epimer steroid epoxides, the ring cleavage reaction of the 16β,17β-epoxide effected with various acid nitriles resulted in the corresponding α,β-acylaminohydroxy compounds in a satisfactory yield, however, the 16α,17α-, the 14,15-epimer epoxides and the 15β,16β-epoxide undergo a rearrangement during the ring cleavage under the experimental conditions of the Ritter reaction, and the formation of the acylamino group does not take place.[16,17]

The ring cleavage of steroid epoxides was extended to the oxethan epimers condensed to ring D. This method provided possibilities for the preparation of α,γ-acylaminohydroxysteroids The 3β-acetoxy-16β,17β-epoxymethyleneandrost-5-ene (1) was reacted with aliphatic and aromatic nitriles in the presence of equivalent

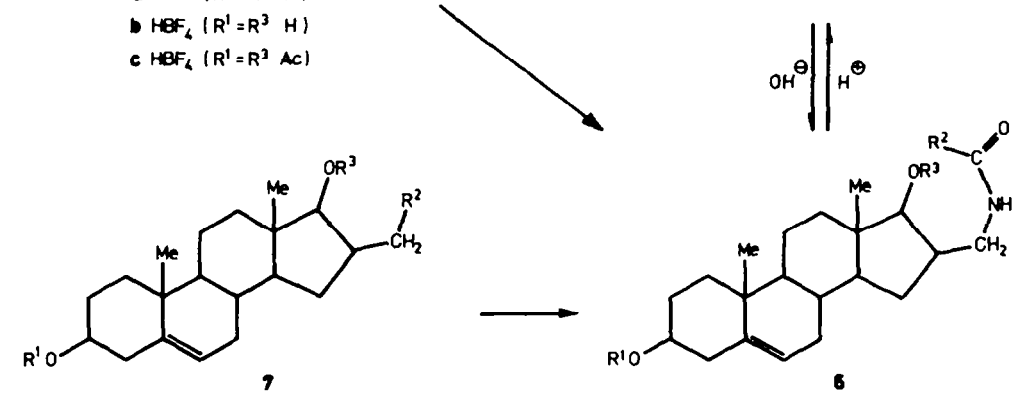
amounts of HBF_4 – diethyletherate and not the α,γ-acylaminohydroxysteroid expected was obtained, but a dihydrooxazine-HBF_4 salt condensed to the sterane skeleton. Employing thus the appropriate nitriles, the derivatives 4a,b,c,e,g,i were prepared. The bases (3a,b,c,e,g,i) can be liberated from the salts formed with an aqueous solution of $NaHCO_3$ The stabilities of the bases are widely different. Compounds 4a and 4b transform relatively readily into the corresponding 3β-acetoxy-16β-acyl-



a (R¹ Ac, R² Me)
b (R¹ Ac, R² CH_2Ph)
c (R¹ Ac, R² c-C_6H_{11})
d (R¹ H, R² c-C_6H_{11})
e (R¹ Ac, R² Ph)
f (R¹ H, R² Ph)
g (R¹ Ac, R² p-C_6H_4Me)
h (R¹ H, R² p-C_6H_4Me)
i (R¹ Ac, R² p-C_6H_4OMe)
j (R¹ H, R² p-C_6H_4OMe)



a (R¹=R³ H)
b HBF_4 (R¹=R³ H)
c HBF_4 (R¹=R³ Ac)



a (R¹=R³ Ac, R² OTs)
b (R¹=R³ Ac, R² N_3)
c (R¹=R³ H, R² N_3)

a (R¹=R³ H, R² Me)
b (R¹=R³ Ac, R² Me)
c (R¹ Ac, R² Me, R³ H)
d (R¹=R³ H, R² CH_2Ph)
e (R¹=R³ Ac, R² CH_2Ph)
f (R¹ Ac, R² CH_2Ph, R³ H)
g (R¹=R³ H, R² c-C_6H_{11})
h (R¹=R³ Ac, R² c-C_6H_{11})

aminomethylandrost-5-ene-17β-ol (6c,6f) on the effect of the $NaHCO_3$ solution, the analogous compounds 3c,e,g,i proved to be stable in the presence of even alkali alcoholates. The relative unstable nature of 3a and 3b is surprising, since substituted dihydrooxazine rings condensed to ring A in the sterane skeleton are usually more stable.[9] In the presence of 1N $NaOCH_3$, compounds 3c,e,g,i transform into

3d,f,h,l via hydrolysis of the 3-acetoxy group at room temperature, while the dihydrooxazine ring remains unchanged. The cyclohexyl derivative 3d can be converted into diol 6g only on refluxing for 8h The aryl-substituted analogues (3f,h,l) did not decompose under such conditions either

The structure of dihydrooxazine steroids and their conversion products were established by spectroscopic methods, in the latter case, the compounds were also synthesized for verification purposes Spectral data confirming the structures assumed for the compounds examined are shown in Tables 1 and 2

Of the data characteristic of structures of type 3 and 4, the νC=N IR band of the dihydrooxazine ring appears between 1630 and 1680 cm^{-1} The H-17 doublet in the ^1H NMR spectrum shows no significant change as compared to the 17-hydroxy compounds (5-7), it appears between 3.5 and 3.9 ppm, (R^2 alkyl), and at about 4.00 ppm (R^2 aryl), resp. In the 17-acetoxy derivatives this signal is at about 4 7 ppm The chemically non-equivalent methylene protons in the hetero ring give double doublets in the intervals 2 8-3 5 and 3 6-3 9 ppm (A and B parts of the ABX spin system, resp.), and the coupling constants deduced for geminal, diaxial and axial-equatorial couplings will be 12-15, 7-11 and 6-8 Hz, resp

Of course, the ^1H NMR signals of R^1 and R^2 can also be identified, thus, e g., the acetylmethyl signals in compounds 3a,c,e,g,i and 4b,i, the methyl signals attached to the hetero ring in 3a and to the aromatic ring in 3g,h, and the methoxy singulet in 3l,l and 4i appear in the interval 2 00-2 05 ppm, at 1 95 and 2 37 ppm, and between 3.8 and 3.9 ppm, resp Furthermore, the signals of the aromatic hydrogens for 3e,f,g,h,i,l and 4b,i can also be determined.

The IR carbonyl band in ester derivatives appears between 1720-1740 cm^{-1} the intense νC-O ester bands are also present at about 1240 cm^{-1} and in the 1000-1150 cm^{-1} range.

Of the ^{13}C NMR data, the downfield signal of the sp^2 carbon atom in the hetero ring should be mentioned confirming structures of type 3 and 4, this appears at about 158 ppm for compounds 3f,g,h and is sensitive to substituent R^2 (in the spectra of 3d and 3l is downfield shifted to 165 0 and 161 9 ppm, resp., thus, electron-donating substitution on the hetero ring decreases the shielding). In salt 4i decreased electron density results in a further significant downfield shift and the signal is found at 169.3 ppm. The shift of the heterocyclic methylene carbon deviates characteristically (44-49 ppm) from that in open-chain derivatives 6 (41-42 ppm) and 7 (53 5 ppm), thus conforming the heterocyclic structure

Like the ^1H NMR spectra, the ^{13}C NMR spectra also contain the signals of the substituents R^1 and R^2: in 3d the cyclohexyl-, in 3f,g,h,l and 4i the phenyl-, in 3g,h,l and 4i the arylmethyl and methoxy signals appear in the shift ranges expected (see Table 2).

Compounds of type 6 are characterized by the IR νNH and Amide-I bands (3450-3300, and 1610-1655 cm^{-1}), the ^1H NMR signal of the NH group (5 5-8 0 ppm) disappearing on the addition of D_2O and the amide carbonyl signal (169-170 ppm) in the ^{13}C NMR spectrum.

Azides 7b,7c are characterized by the IR band at about 2100 cm^{-1}.

In all new steroid derivatives, the NMR characteristics of the skeleton can be identified· in the ^1H NMR spectra, the C-18 and C-19 methyl singlets (at 0.67-0 86 and 0 95-1.08 ppm), the H-5 olefin signal (5.26-5.44) and the signals of H-3 and H-17 adjacent to oxygen The latters are shifted paramagnetically by about 1 ppm in the acetoxy derivatives as compared to the corresponding hydroxyl derivatives In the ^{13}C NMR spectra, the signal of all skeletal carbons can be identified, these were assigned by comparing the analogous data, by employing literature data,[18] and by establishing the order of carbon atoms belonging to the individual signals by DEPT (Distortionless Enhancement by Polarization Transfer) experiments.[19,20]

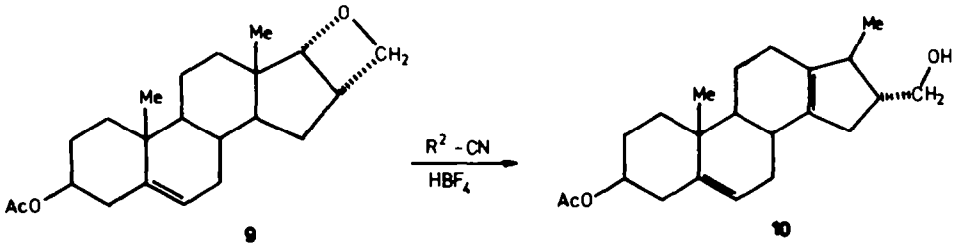
Table 1 The most important IR (in KBr discs, cm^{-1}) ^1H NMR data (in $CDCl_3$ solution $\delta_{TMS}=0$ ppm) of compounds 3a c-j 4b i 5a-c 6a-h and 7b c at 250 MHz

Compound	νNH νN$_3$[a]	νC=O (ester)	amide I νC=N[b]	CH$_3$(19) s(3H)	CH$_3$(19) s(3H)	CH$_3$(Ac and R^2) s (3H)	CH$_2$(16) m (2H)[c]	CH$_2$ s(2H)	H-3 m(1H)	H-6 d(1H)[d]	H-17 d(1H)[e]	ArH s(5H)[f]	NH s(1H)
3a	–	1730	1680	0 75	1 05	1 95[g] 2 05	~3 4	–	~4 6	5 35	~3 9	–	–
3c[h]	–	1730	1680	0 80	1 05	2 03	~2 80 3 65	–	4 55	5 33	3 73	–	–
3d[h]	–	–	1668	0 74	1 02	–	2 78 3 66	–	3 50	5 34	3 76	–	–
3e	–	1735	1650	0 83	1 04	2 02	3 05 3 90	–	4 55	5 40	4 02	7 35	–
3f	–	–	1639	0 84	1 03	–	3 04 3 89	–	3 52	5 35	4 02	~7 4	–
3g	–	1734	1634	0 83	1 04	2 04 2 37[l]	3 02 3 88	–	4 60	5 38	4 00	7 18 7 85	–
3h	–	–	1647	0 83	1 03	2 37[l]	3 02 3 90	–	3 52	5 34	4 00	7 18 7 84	–
3i	–	1735	1650	0 83	1 05	2 03 3 82[j]	3 00 3 80	–	4 55	5 35	3 96	6 83 7 88	–
3j	–	–	1640	0 84	1 03	3 83[j]	3 01 3 85	–	3 52	5 35	4 00	6 89 7 92	–
4b[k]	–	1732	1676	0 54	1 00	2 03	~4 05	3 76	~4 6	5 35	4 35	7 36	10 8
4i[k]	–	1720	1645	0 85	1 05	2 04, 3 89[j]	3 24 4 6	–	4 60	5 40	4 14	7 02 8 03	10 4
5a	–	–	–	0 86	1 08	–	3 10 3 30	–	3 65	5 42	3 96	–	–
5b[k]	–	–	–	0 69	0 97	–	~3 0 ~3 30	–	~3 45	~5 3	~3 65	–	–
5c[k]	–	1738	–	0 82	1 02	2 03	~3 3 ~3 55	–	~4 60	5 37	~3 70	–	–
6a[l]	3354	–	1612	0 67	0 95	1 79	~3 0 ~3 25	–	~3 55[m]	5 26	~3 55[m]	–	7 52
6b	~3300	1730	1647	0 84	1 02	1 93 2 03 2 09	~3 28	–	4 60	5 36	4 74	–	5 72
6c	~3400	1728	1653	0 78	1 02	1 97 2 03	~3 25 ~3 50	–	4 60	5 36	3 77	–	6 63
6d[n]	3418	–	1636	0 69	1 00	–	3 15 ~3 50	3 55	~3 50	5 35	3 65	7 26	6 15
6e[l]	3430	1734	1655	0 75	0 97	1 97[o]	~3 0 ~3 3		4 45	5 35	4 65	7 24	7 83
6f	3380 3317	1734	1639	0 67	1 01	2 03	3 18 ~3 50	3 55	4 58	5 35	3 66	7 27	6 22
6g	3400	–	1641	0 77	1 01	–	~3 25 ~3 5[m]	–	~3 5[m]	5 35	3 75	–	6 45
6h	~3350	1734	1645	0 84	1 02	2 03 2 07[p] 2 09[p]	~3 3	–	4 60	5 36	4 74	–	5 60
7b	2100 2110	1724 1738	–	0 82	1 03	2 03 2 10	3 20 3 35	–	4 60	5 38	4 83	–	–
7c	2104	–	–	0-78	1 02	–	3 29 3 58	–	3 52	5 35	3 78	–	–

The HBF_4 salt 4a decomposed in aqueous dioxane at room temperature and 16α-amino-methyl-3β,17β-diacetoxyandrost-5-ene HBF_4 salt (5c) was formed. The dioxane solution of 5c with $NaHCO_3$ transformed into 6c The conversion, in accordance with the N → O acyl migration reaction of 1,3-aminoalcohols, is reversible,[21] and, in the presence of fluoroboric acid, assumably via the intermediate 8, it yields 5c again. Thus, compound 3 obtained in the ring-expansion reaction of the steroid oxethane can be regarded as an intermediate in the N → O acyl migration reaction of 1,3-amino-alcohols stabilized under kinetic control Compound 5b was preparedby the conversion of 3β,17β-diacetoxy-16β-p-toluenesulfonyl-oxymethyl-androst-5-ene (7a) having a configuration confirmed earlier[22] into 7b with NaN_3, followed by hydrolysis into 7c and subsequent reduction with hydrazine hydrate in the presence of Raney nickel The ring-expansion reaction of non-condensed oxiranes and oxethanes – under the condition of the Ritter reaction, yielding the corresponding oxazolines and dihydrooxazines – are known [23-26] The stereochemical conditions, however, are lacking for ring expansion of oxiranes condensed to the sterane skeleton into oxazolines. Conversion of steroid oxiranes into dihydrooxazines via a secondary reaction of free hydroxyl groups in the molecule has already been observed in the case of 3β-hydroxy-4,5-epoxycholestan epimers.[9] During the conversion of 16α,17α,21-trihydroxy-9β,11β-epoxy-4-pregnene, the 5α,9α-dihydroxyoxazine ring is formed, owing to the presence of the 4,5-unsaturated double bond [15]

Compound 1 investigted by us transformed into oxonium ion in acid media, at which the substitution of the nucleophilic alkyl- or arylnitril can take place at both the 16-methylene and the 17-carbon atom The attack at C-16 is favoured sterically, and the carbonium cation developed forms a dihydrooxazine ring condensed to the sterane skeleton in an intramolecular reaction with the 17-hydroxy group The nucleophilic attack at C-17 would involve inversion, and stabilization of the carbonium cation formed would yield the 16β-hydroxymethyl-17α-acylaminosteroid Its occassional cyclization would lead to the sterically unfavoured trans anellated dihydrooxazine The 16β,17β-epoxymethylene ring can favourably be attacked in a nucleophilic reaction, thus it is justified that in the Ritter reaction the nitrogen function is attached to the primary carbon atom, unlike the general observation assuming the attack at the carbon atom of higher order [3]

The Ritter reaction of the epimeric compound 9, however, yields the cleavage of the oxethane ring followed by stabilization of the carbonium cation developed by the Wagner-Meerwein rearrangement Under such conditions, the attack by the nitril funciton is missing, and 3β-acetoxy-16α-hydroxymethyl-17β-methyl-18-nor-androst-5,13(14)-diene (10) is formed



9 10

Notes to Table 1 [a] νNH (6a-h) or νN_3 band (7b,c), [b] νC=N (3a,c-l, 4b,l) or amide-I band (6a-h), [c] AB part of an ABX multiplet (J_{AB} 12-15, J_{AX} 7-11 and J_{BX} 6-8 Hz), [d] J 4 2-5 2 Hz, [e] J 9 5-10 5 Hz, [f] AA'BB' multiplet of 4H intensity (3g,h,k,l, and 4l), [g] Methyl group on the heteroring, t (∿1 Hz, long range coupling), [h] Overlapping multiplets of cyclohexyl protons of 11H intensity 1 0-2 4 ppm, [i] Methyl group on the benzene ring, [j] Methoxy group, [k] HBF_4 salt giving broadened signals, [l] Solvent DMSO-d_6, [m] Overlapping signals, [n] Data measured for a sample containing a significant amount of impurities, [o] Two overlapping lines (6H), [p] Split due to hindered rotation

Table 2 ^{13}C NMR chemical shifts on compounds 3d, f, g, h, j, 4i, 6b, c, g, h and 7b, c (δ_{TMS} = 0 ppm) in $CDCl_3$ solution, at 63 MHz

Compound	3d[a,b]	3f[c]	3g[c,d]	3h[c]	3j[a,c]	4i[c,d]	6b[d]	6c[d]	6g[b]	6h[a,b,d]	7b[d]	7c
C-1[e]	37 6	37 5	37 3	37 5	37 5	37 2	37 1	37 2	37 6	37 2	37 2	37 5
C-2	31 9[f,g]	31 9[g]	28 0	31 8[g,h]	31 9[g,h]	27 9	27 9	28 0	31 9[g,h]	27 9	27 9	31 8[g,h]
C-3	71 6	71 7	74 0	71 7	71 7	73 8	73 9	74 0	71 9	73 9	73 9	71 8
C-4	42 5	42 5	38 3	42 5	42 5	38 3[e]	38 2	38 3	42 6	38 3	38 3[g]	42 5
C-5	141 4	141 3	140 2[g]	141 3	141 3	140 3	140 1	140 1	141 2	140 1	140 1	141 2
C-6	121 0	121 1	122 1	121 0	121 0	121 7	122 0	122 2	121 3	122 0	122 0	121 2
C-7	30 9[g]	31 6[i]	31 6[i]	31 5[g]	31 6[g,j]	31 5[g,h]	30 9[g]	30 4[g]	30 4[g]	30 8[g]	30 8[i]	30 8[g]
C-8	31 6	31 7[i]	31 7[i]	31 6[g]	31 6[g,j]	31 5[g,h]	31 3[g]	31 5	31 6	31 3	31 4	31 5
C-9	50 7[i]	50 7[k]	50 6[k]	50 6[i]	50 6[i]	50 2[i]	50 2[h]	50 4[h]	50 6[i]	50 2[h]	50 2[k]	50 4[i]
C-10	36 8	36 8	37 0	36 8	36 8	36 9	36 8	36 9	36 9	36 9	36 9	36 8
C-11	20 7	20 7	20 7	20 7	20 7	20 5	20 6	20 8	20 9	20 6	20 6	20 8
C-12[e]	37 8	37 9	37 9	37 9	37 9	37 1	37 6	37 7	37 8	37 7	37 6	37 7
C-13	44 0	44 3	44 3	44 2	44 3	44 0	43 5	43 9	44 0	43 5	43 5	43 9
C-14	49 5[i]	49 7[k]	49 7[k]	49 7[i]	49 7[i]	49 1[i]	50 2[h]	50 4[h]	50 7[i]	50 2[h]	50 3[k]	50 5[i]
C-15	31 9[f,g]	32 0[g,h]	31 9[i]	32 0[g]	31 9[g,h]	31 0[g]	31 7[g]	31 9[g]	31 9[g,h]	31 8[g]	31 7[i]	31 8[g,h]
C-16	31 9[f,g]	32 0[g,h]	32 1[i]	31 8[g,h]	32 2[g]	31 1[g]	39 0	41 4[i]	41 1[k]	39 2	38 7[g]	40 3
C-17	84 7	85 7	85 6	85 6	85 7	91 6	82 6	82 1	82 5	82 6	81 9	81 5
C-18	13 0	13 2	13 2	13 2	13 2	13 2	13 0	12 3	12 3	13 0	12 9	12 2
C-19	19 5	19 5	19 4	19 5	19 5	19 4	19 4	19 4	19 5	19 4	19 4	19 5
CH_2(16)	44 2	49 0	48 9	48 9	48 7	44 5	41 4	41 0[i]	41 2[k]	41 1	53 4	53 6
OC=N/NC=O[l]	165 0	158 0	158 1	158 2	161 9	169 3	169 8	170 1[k]	176 0	175 9	–	–
CH_3[m]	–	–	21 3[n]	21 4	55 4	56 0	23 2	23 4	–	–	–	–

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EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected Specific rotation was measured with POLAMAT-A polarimeter in chloroform, c=1 Other solvents are indicated

Layer chromatograms were obtained on Kieselgel-G (Merck) layers of 0 5 mm layer thickness The developing agents were methanol benzene (10.90), methanol benzene (5 95) The detection was effected by spraying with 50 % aqueous phosphoric acid with subsequent heating at 100-120 °C for 15 minutes The R_f values were determined on the basis of spots observed during illumination with UV light of 365 nm In the column chromatographie separation, Al_2O_3 standardized according to Brockmann with activity III-IV was used.

The ^1H NMR spectra were recorded in an 5 mm tube at room temperature on a Bruker WM-250 FT spectrometer controlled by an Aspect 2000 computer at 250 13 MHz, in $CDCl_3$ solution using the deuterium of the solvent as the lock and TMS as internal standard The most important measuring paremeters of the ^1H NMR spectra are as follows sweep with 5 kHz, pulse with 1 μs (∿20° flip angle), acquisition time 1 64 s, number of scans. 16 or 32, computer memory 16 K Lorentzian exponential multiplication for signal-to-noise enhancement (line width 0 7 Hz) were applied

The ^{13}C NMR spectra were run in 5 mm tubes, at room temperature on a Bruker WM-250 FT spectrometer controlled by an Aspect 2000 computer at 62.9 MHz in chloroform solution using the deuterium signal of the solvent as the lock and TMS as internal standard The most important measuring parameters are sweep width 16 kHz, pulse width 5 μs (∿25°flip angle), acquisition time 0 51 s, number of scans 2K-4K, computer memory 16 K Complete proton noise decoupling (∿2 5-3W) and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 2 0 Hz)

DEPT experiments were performed running three spectra with 45, 90 and 135° theta-pulses, respectively, and editing subspectra by linear combination of the former ones The 90° pulse length were 10 8 and 22 5 μs for ^{13}C and ^1H nuclei in the 10 mm probehead After every scan, 3 s delay was inserted allowing protons to relax

3β-Acetoxyandrost-5-ene-2′-R^2-(16β,17β-e)-2H-oxazine HBF_4 (4a,b,c,e,g,l)

(General method 1)

Compound 1 (1 g, 3 mmol) was dissolved in CH_2Cl_2 and acid nitrile (5 g) was added to it The solution was cooled to 0 °C and HBF_4.diethylether was added (0 5 ml, 3 mmol) to it under stirring, dropwise The reaction mixture was allowed to stand at room temperature for 6h, then anhydrous diethyl ether (100 ml) was added to it The crystalline substance separated from the reaction mixture on standing for 24 h was filtered off then recrystallized from a mixture of CH_2Cl_2 and diethyl ether (Table 3)

Notes to Table 2. [a] Assignment was proved by DEPT experiment, [b] Signals of the cyclohexyl ring (the C-2′,6′ and C-3′,5′ pairs are chemically non-equivalent due to molecular asymmetry): CH_2· 26 0, 26.1, 26 2 and 30 1[h] (3d), 26 0[f] and 29 9[h] (6g), 25 9[f], 29 8 and 29 9 (6h), CH: 48.6 (3d), 45 8 (6g), 45 7 ppm (6h) [c] Signals of the aromatic carbons C-1′, C-2′, C-3′,5 and C-4′ 134 2, 127.4, 128 1 and 130 5 (3f), 131 6, 128 8, 127 4 and 140.6[g] (3g), 131.4, 128 8, 127 3 and 140 6 (3h), 126 5, 129 0, 113 6 and 158 2 (3l), 116 9, 131.4, 115 4 and 166 4 ppm (4l) [d] Signals of the methyl and carbonyl carbons of the acetoxy groups: 21 2[n] and 170.2 (3g), 21.1 and 170 3 (4l), 20 9, 21 3 and 170 4, 171 1 (6b), 21 3 and 170.4[k] (6c), 20 9 21 3 and 170.3, 171 0 (6h), 20 9, 21 3 and 170 3, 170 6 ppm (7b). [e,g,i,k,n] Assignment may be interchanged [f] Three or [h,j] two overlapping lines, [l] Signal of sp^2 carbon in the heteroring (3d,f,g,h,j, 4l) or of the amide carbonyl (6), [m] Methyl signal of the methyl (3g,h) or methoxy (3l,4l) group attached to the R^2-phenyl ring or of the acetamino group (6b,c)

Table 3 Physical and analytical data on compounds 3a,c-l, 4a-c,e,g,l, 5a-c, 6a-h and 7b,c

Compound	Formula	Molecular weight	M p (°C)	$[\alpha]_D$	R_f	Yield (%)	Analysis (%) Calculated	C	H	N
3a	$C_{24}H_{35}O_3N$	385 54	195-198	- 12	0 80[b]	86	Calculated	74 76	9 15	3 63
							Found	74 55	9 32	3 50
3c	$C_{29}H_{43}O_3N$	453 67	165-168	- 23	0 85[b]	98	Calculated	76 77	9 55	3 09
							Found	76 50	9 43	3 27
3d	$C_{27}H_{41}O_2N$	411 63	189-192	- 13	0 40[b]	98	Calculated	78 78	10 03	3 40
							Found	78 55	10 16	3 27
3e	$C_{29}H_{37}O_3N$	448 63	172-175	- 35	0 95[c]	98	Calculated	77 64	7 76	3 12
							Found	77 45	7 40	3 02
3f	$C_{27}H_{35}O_2N$	405 58	193-196	- 31	0 60[c]	95	Calculated	79 95	8 69	3 45
							Found	79 82	8 55	3 10
3g	$C_{30}H_{39}O_3N$	461 65	186-190	- 31	0 90[c]	98	Calculated	78 05	8 51	3 03
							Found	78 28	8 36	3 15
3h	$C_{28}H_{37}O_2N$	419 61	178-181	- 27	0 55[c]	95	Calculated	80 14	8 88	3 33
							Found	79 95	8 95	3 06
3l	$C_{30}H_{39}O_4N$	477 65	195-200	- 24	0 85[c]	100	Calculated	75 43	8 23	2 93
							Found	75 36	8 38	2 65
3l	$C_{28}H_{37}O_3N$	435 61	227-231	- 25	0 50[c]	95	Calculated	77 20	8 50	3 21
							Found	77 32	8 43	3 05
4a	$C_{24}H_{36}O_3NBF_4$	473 37	206-210	- 4	-	98	Calculated	60 89	7 66	2 95
							Found	60 73	7 78	3 05
4b	$C_{30}H_{40}O_3NBF_4$	549 47	169-174	- [a]	-	75	Calculated	65 57	7 33	2 54
							Found	65 38	7 54	2 35
4c	$C_{29}H_{44}O_3NBF_4$	541 50	197-201	- 5	-	95	Calculated	64 32	8 19	2 58
							Found	64 45	8 35	2 52
4e	$C_{29}H_{38}O_3NBF_4$	535 45	212-214	- 27	-	100	Calculated	65 05	7 15	2 61
							Found	65 28	7 35	2 48
4g	$C_{30}H_{40}O_3NBF_4$	549 47	212 215	4	-	98	Calculated	65 57	7 33	2 54
							Found	65 35	7 24	2 30
4l	$C_{30}H_{40}O_4NBF_4$	565 47	213-218	12	-	96	Calculated	63 72	7 13	2 47
							Found	63 80	7 05	2 65
5a	$C_{20}H_{33}O_2N$	319 49	245-250[d]	- 36[e]	-	92	Calculated	75 18	10 41	4 38
							Found	75 27	10 35	4 52
5b	$C_{20}H_{33}O_2N\ HBF_4$	407 32	260-265[d]	- 38[e]	-	91	Calculated	58 97	8 41	3 43
							Found	58 85	8 35	3 08
5c	$C_{24}H_{37}O_4N\ HBF_4$	491 93	195-198[d]	- 14[e]	-	88	Calculated	58 66	7 79	2 85
							Found	58 47	7 85	3 02
6a	$C_{22}H_{35}O_3N$	361 52	280-282	- 61	0 25[b]	84	Calculated	73 08	9 75	3 87
							Found	73 25	9 61	3 60
6b	$C_{26}H_{39}O_5N$	445 61	183-185	- 42	0 50[b]	96	Calculated	70 08	8 82	3 14
							Found	70 27	8 65	3 02
6c	$C_{24}H_{37}O_4N$	403 56	239-240	- 79	0 40[b]	82	Calculated	71 42	9 24	3 47
							Found	71 26	9 08	3 32
6d	$C_{28}H_{39}O_3N$	437 63	210-215[d]	- [a]	0 20[b]	80	Calculated	76 84	8 98	3 20
							Found	76 70	8 72	3 08
6e	$C_{32}H_{43}O_5N$	521 70	225-230[d]	- 11	0 80[c]	95	Calculated	73 67	8 30	2 68
							Found	73 58	8 18	2 50
6f	$C_{30}H_{41}O_4N$	489 66	222-226	- 16	0 40[b]	72	Calculated	73 58	8 44	2 86
							Found	73 35	8 15	2 70
6g	$C_{27}H_{43}O_3N$	429 65	233-237[d]	- 57	0 30[b]	75	Calculated	75 47	10 08	3 26
							Found	75 22	9 92	3 42
6h	$C_{31}H_{47}O_5N$	513 72	160-164	- 38	0 60[c]	96	Calculated	72 47	9 22	2 72
							Found	72 30	9 02	2 55
7b	$C_{24}H_{34}O_4N_3$	429 56	95-97	- 52	-	95	Calculated	67 11	7 98	9 94
							Found	66 95	8 30	9 50
7c	$C_{20}H_{31}O_2N_3$	345 49	107-109	- 55	-	88	Calculated	69 52	9 04	12 16
							Found	69 65	9 18	12 27

Notes [a] Unsoluble, [b] Methanol benzene (10 90), [c] Methanol benzene (9 95), [d] Decomposition, [e] In glacial acetic acid, c = 1

3β-Acetoxyandrost-5-ene-2′-R^2-(16β,17β-e)-2H-oxazine (3a,c,e,g,l) (General method 2)

Compound 4a,c,e,g,l (2 mmol) was dissolved in CH_2Cl_2 (10 ml), then a saturated aqueous solution of $NaHCO_3$ was layered over it and they were allowed to stand at room temperature for 2h The organic phase was separated, washed with wather, dried and evaporated to dryness The residue was recrystallized from a mixture of acetone and petroleum ether (Table 3)

3β-Acetoxyandrost-5-ene-2′-R^2-(16β,17β-e)-2H-oxazine HBF_4 (4a,b,c,e,g,l) alcoholic hyrolysis (General method 3)

a Compound 4a,b,c,e,g,l (2 mmol) was dissolved in CH_2Cl_2 (10 ml), then a saturated aqueous solution of $NaHCO_3$ was layered over it and they were allowed to stand at room temperature for 24h The organic phase was separated, washed with water, dried and evaporated to dryness Under such conditions, 4a and 4d decomposed into 6c and 6f Compounds 4c,e,g,l transformed into the corresponding steroid bases (3c,e,g,l) (Table 3)

b Compound 4a,b,c,e,g,l (2 mmol) was dissolved in methanol (25 ml) and refluxed with $NaHCO_3$ (0 220 g, 4 mmol) for 1h The reaction mixture was diluted with water, saturated with $(NH_4)_2SO_4$ and the crystalline precipitate was filtered off then crystallized from a mixture of acetone and water Under such conditions, 4a and 4b decomposed into 6a and 6d Compound 4c yielded a 3 1 mixture of 3d and 6g, which can be separated chromatographically using a 1 1 mixture of chloroform and benzene Compounds 4c,e,g,l undergoes desacetylation in alkaline media yielding 3d,f,h,l, the dihydrooxazine ring remained unchanged (Table 3)

16β-N-acylaminomethyl-3β,17β-diacetoxyandrost-5-ene (6b,e,h) (General method 4)

Compound 6a,d,g (2 mmol) was allowed to stand in a mixture of acetic anhydride (5 ml) and pyridine (5 ml) overnight It was then diluted with water, and crystalline precipitate separated was recrystallized from a mixture of methanol and water (Table 3)

16β-Azidomethyl-3β,17β-diacetoxyandrost-5-ene (7b)

Compound 7a |Ref 22| (1 1 g, 2 mmol) was dissolved in dimethylformamide (20 ml), NaN_3 (1 3 g, 20 mmol) was added to it and the reaction mixture was kept on a water bath at 100 °C for 2h It was then diluted with water, the crystalline precipitate separated was recrystallized from a mixture of methanol and water (Table 3)

16β-Azidomethyl-3β,17β-dihydroxyandrost-5-ene (7c)

$NaOCH_3$ (0 110 g, 2 mmol) was added to a solution of 7b (0 860 g, 2 mmol) in methanol and the solution was refluxed for 1h It was diluted with water, the crystalline precipitate separated was crystallized from a mixture of methanol and water (Table 3)

16β-Aminomethyl-3β,17β-dihydroxyandrost-5-ene (5a) and 16β-aminomethyl-3β,17β-dihydroxyandrost-5-ene HBF_4 (5b)

Compound 7c (0 690 g, 2 mmol) was dissolved in ethanol (50 ml) then hydrazine hydrate (2 5 ml, 50 mmol) and Raney-Ni catalyst (20 mg) were added to it The reaction mixture was allowed to stand at room temperature for 6h then the catalyst was filtered off The reaction mixture was diluted with water, the crystalline precipitate separated was filtered off, washed with water unil neutral and dried

Compound 5a (0 320 g, 1 mmol) was suspended in CH_2Cl_2 (2 ml), HBF_4 Et_2O (0 8 ml, 5 mmol) was added to it, then the reaction mixture was diluted with anhydrous diethyl ether The white crystalline precipitate was filtered off and dried in vacuum desiccator (Table 3)

16β-Aminomethyl-3β,17β-diacetoxyandrost-5-ene HBF_4 (5c)

a Compound 4a (0 473 g, 1 mmol) was dissolved in dioxan (20 ml), some drops of water were added to it and the solution was allowed to stand for 24h The reaction mixture was diluted with water, the precipitate separated was filtered off then the recrystallized from a mixture of CH_2Cl_2– diethyl ether (Table 3)

b Compound 6c (0 020 g, 0 05 mmol) was dissolved in dioxan (3 ml), then HBF_4 Et_2O (0 3 ml, 2 mmol) was added to it and the solution was kept at 80 °C for 6h After cooling, diethyl ether (50 ml) was added to it and the fine precipitate was filtered off 5c 0 012 g (60 %)

3β-Hydroxy-16α-hydroxymethyl-17β-methyl-18-nor-androst-5,13(14)-diene (10)

Compound 9 (1 g, 2 mmol) was converted with acetonitrile (5 g) into the non-crystallizing 3β-acetoxy-16α-hydroxymethyl-17β-methyl-18-nor-androst-5,13(14)-diene under the condition given for General method 1 The crude reaction product was dissolved in methanol (25 ml), $NaHCO_3$ (0 220 g, 4 mmol) was added to it, refluxed for 1h to achive desacetylation into 10
9 0 790 g (87 0 %) M p 154-158 °C (lit[26] 153-156 °C)

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